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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/924,400 | 08/07/2001 | Tony N. Frudakis | 210121.419C12 | 7385 |

500 7590 12/29/2005

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| EXAMINER | |
|---|---|
| ZEMAN, MARY K | |
| **ART UNIT** | **PAPER NUMBER** |
| 1631 | |

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/924,400 | FRUDAKIS ET AL. | |
| | Examiner | Art Unit | |
| | Mary K. Zeman | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *3,4,11,15 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,11,15 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/19*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *12/12*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's arguments filed 10/03/05 have been fully considered but they are not persuasive.

Claims 3, 4, 11, 15 and 18 are pending in this application.

The IDS filed 8/19/05 has been entered and considered.

The Examiner proposed amendments 12/12/05 to put the case in condition for allowance, however, as of the time of this action, no response had been received. See Attached.

### *Claim Rejections - 35 USC § 112*

Claims 3, 4, 11, 15 and 18 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 has been amended to recite "a sequence that varies from SEQ ID NO: 302 due to differences in codon usage as a result of the degeneracy of the genetic code." This amendment was made in an attempt to overcome the rejections of record. This phrase remains vague and indefinite as one of skill in the art would not be apprised of the limits of this claim. What differences are encompassed? The examiner proposed the following claim as overcoming this rejection in a telephone interview:

"18. An isolated cDNA comprising a sequence selected from the group consisting of:

(a) the sequence provided in SEQ ID NO: 302, or an isolated cDNA sequence encoding the polypeptide of SEQ ID NO: 305;

(b) the sequence provided in SEQ ID NO: 303, or an isolated cDNA sequence encoding the polypeptide of SEQ ID NO: 306; and

(c) the full length complement of the sequence provided in SEQ ID NO: 302 or 303."

However, as of the date of this action, this amendment had not been accepted by Applicant, nor had any further amendments been made.

The Examiner believes Applicant intends to encompass different, but equivalent cDNAs which encode the same polypeptide sequences as encoded by SEQ ID NO: 301 and 302.

However, the claim is not limited to that interpretation. A variant of the claimed sequence does not appear to be specifically defined in the specification, and one of skill in the art would not be apprised of how different a sequence may be from the base sequence and still be included within the scope of the claims.

Applicant argues that one of skill in the art clearly understands the scope of the invention, and provides a textbook reference. This argument is not persuasive. This textbook does not appear to be referenced in the specification, nor is the examiner able to support this limited definition with a reading of the specification. At page 26 of the specification, "degenerate variants" are described as "encoding immunogenic polypeptides", taking into account "codon degeneracy, amino acid similarity, reading frame positioning and the like... variants will contain one or more substitutions, additions, deletions and/or insertions, preferable such that the immunogenicity of the polypeptide encoded is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein. The term "variants" should also be understood to encompass homologous genes of xenogenic origin." Further in the specification at page 30, "nonetheless polynucleotides that vary due to differences in codon usage are specifically contemplated... alleles of the genes comprising the sequences... that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function..." Therefore, the limited definition set forth in the textbook reference is not representative of the invention as described in the specification, and the term "degenerate variants thereof" is unclear as to the specific polynucleotides encompassed within its scope.

Claims 3, 4, 11 and 15 depend from claim 18.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 4, 11, 15 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 (CAFC 1988). The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below which leads to the determination that the above claims lack enablement due to undue experimentation being required to make and use the invention.

For enablement purposes, the experimentation which is necessary must be directed to the requirements under 35 USC 112, first paragraph, as summarized in the MPEP in 2162 which states that "the patentee must disclose in the patent sufficient information to put the public in possession of the invention and to enable those skilled in the art to make and use the invention." Thus, both making the invention must be enabled as well as a use thereof. The MPEP further summarizes these requirements in section 2164.01 in the "Test of Enablement" via stating that "Accordingly, even though the statute does not use the term 'undue experimentation,' it has been interpreted that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation." The MPEP further states in section 2164.01 that "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." Further, "The test of enablement is not whether any experimentation is necessary, but whether if experimentation is necessary it is undue." The MPEP then summarizes the below factors for the determination of the enablement requirement in 2164.01(a) as also set forth above as the so called Forman Factors. In the MPEP at section 2164.01(b), third paragraph, a key issue that can arise in the biotechnical area is the

availability of starting materials to make the invention, especially when such availability is present "only after extensive screening." The MPEP at section 2164.01(c) further summarizes that requirement of a use for the claimed invention is included either as recited or based on knowledge of similar inventions, described as exemplified in relationship to compounds. Lastly, it is acknowledged that the specification does not need to disclose what is well known to those skilled in the art as described in the MPEP at section 2164.05(a), 6th paragraph.

The MPEP at 2164.04 requires that it is necessary to firstly construe the claims before any analysis of enablement can occur. Thusly the above rejected claims 3, 4, 11, 15 and 18 are construed to be directed to the polynucleotides of SEQ ID NO: 302 or 303 or sequences that varies from SEQ ID NO: 302/303 due to differences in codon usage as a result of the degeneracy of the genetic code. These polynucleotides are cDNA's that are alleged to encode immunogenic polypeptides. The claims also comprise complements of the sequence. In the previous response, Applicant asserts that degenerate variants thereof mean only polynucleotides which encode the same polypeptide sequence but utilizing differing equivalent codons. This polypeptide is construed as being prepared via host cell culturing wherein the host cell contains a vector which in turn contains a polynucleotide made up of normally found nucleotides which encode the polypeptide of SEQ ID NO: 302 or 303 via the translation of normally occurring triplet codons therein into said polypeptide.

Given the above summaries, it is appropriate to turn to consideration of the factors determinative of enablement regarding whether undue experimentation is required to enable the claimed invention.

The eight factors are summarized below regarding supporting the above rejection.

(1) – the quantity of experimentation necessary-

There are an enormous number of polynucleotides, vectors, and host cells to be experimentally tested in order to make a useful polypeptide encoded by SEQ ID NO: 302 or 303 or degenerate variants thereof. Regarding the polynucleotides to be tested, the art recognizes that for each amino acid in the encoded polypeptides that there are degenerate codons available as shown in the well known Biochemistry textbook by Lehninger as in Table 31-5 on page 718. Counting the number of codons results in observing that 5 of the normal amino acids may each be encoded by one of 4 three nucleotide codon options. For 9 of the normal amino acids, 2 such

three nucleotide codon options are available. For 3 amino acids, 6 such codon options are available. For 1 amino acid, 3 such codons are utilized. For 2 amino acids, only one such codon is available. An average of the number of codons per amino acid may be approximated via an averaging of the above codon usage as being three available codons for an average amino acid. Without specifying the length of SEQ 302 or 303 (polynucleotide), it may be reasonably approximated that the encoded polypeptides are a polypeptide which falls within the range of polypeptides with sizes as shown in the well known Biochemistry textbook by Lehninger as in Table 3-2 on page 57. A median polypeptide contains 550-800 amino acids. Choosing conservatively, a median polypeptide thus contains 500+ amino acids. Therefore, an estimate of the number of potential polynucleotides encoding a polypeptide of 500 amino acids would be that calculated at 3 raised to the $500^{th}$ power. This further calculates to approximately $10^{240}$ possible polynucleotides to evaluate or experimentally test to find those useable in making a useful polypeptide, or a polypeptide meeting the limits of the genus of polypeptides encoded by claims 18. Thus, there is an enormous number of polynucleotides to experimentally test to find any that encode the polypeptides or its variants which are useful. The art of polypeptide usage in Biotechnology utilizes polypeptides via some type of enzymatic activity or binding activity. Claim 18 lacks citation of any such usefulness or activity limitation. Thus, another experimentation requirement regarded to enable the use of the instantly claimed methods is the determination of a useful activity for SEQ 302/303. The file history indicates that a polypeptide of encoded by the sequence of exactly SEQ ID NO: 302 or 303 is useful in an antibody binding assay for diagnosing breast cancer. An antibody assay is strongly dependent on the three dimensional structure of the polypeptide. In the well known Biochemistry textbook by Lehninger at pages 58-62, not only is the vast diversity of protein polypeptides set forth regarding functionality, such as enzymatic function, but that each protein has a characteristic three-dimensional shape referred to as its conformation. The claims have not disclosed what function to test which alone relegates the experimentation to undue experimentation regarding a lack of any indication of what experimental test or assay is to be performed. This experimental search for a test is further complicated by a lack of any guidance regarding what single, or even a subset of polynucleotides out of the $10^{240}$ should be tested. These considerations are supportive of a determination of undue experimentation to find a starting material polynucleotide to be

placed in a vector and in turn a host cell for culturing, for production of a polypeptide to be used as claimed.

Turning to the question of what host cell is to be utilized in producing the polypeptide, it is well known that a myriad of thousands of cell types are known to Biotechnology. It is acknowledged that some of these known cell types are more commonly utilized for host cell culturing as described in the specification. Even such commonly utilized host cells number into the hundreds. In USP 5,082,767, Hatfield et al., the expression of polynucleotides in host cells of various types is described in column 1 lines 1-49. Even though such expression practices are frequently carried out, Hatfield et al describe another major problem in this area in column 1 lines 50-65, wherein a protein (or polypeptide) is produced in recoverable quantities, but is inactive. As discussed above, some type of activity is required for the polypeptide encoded by SEQ ID NO: 302 or 303 to be used in the disclosed methods. A solution is described in Hatfield et al in column 1 lines 61-65 as elusive and is apparently related to an unpredictability in proper protein folding during expression. In column 1 line 66 through column 2 line 59, various codon usage and context effects are described as problematic. In column 2 lines 53-59 the predictive value of statistical rules for preferred nucleotides adjacent to codons is described as relatively low. Hatfield et al go on to analyze codon pair usage frequencies wherein optimization of codon pair usage is then derived for determining polynucleotides which encode a protein or polypeptide in order to achieve an active polypeptide when made via a host cell culture such as described herein. This process, however, is complex and requires very specific host cell and polypeptide correspondence in order to perform the analysis to then make a useful and active protein. It is noted that the instant disclosure lacks any codon pair frequency analysis description for even a single host cell type. The Hatfield et al disclosure is a single procedural description which still lacks indication of how someone of skill in the art would find an activity assay to utilize for a polypeptide encoded by SEQ ID NO: 302 or 303 to determine a predictable activity on which to base the codon usage analysis as disclosed therein. Thus, there would be no predictability as to what to direct a codon pair usage determination to as set forth in Hatfield et al. for the making of an active polypeptide. It is also pointed out that Hatfield et al. is a single disclosure and as such is not a well known practice for enabling the instant invention, and thus not available to applicant on this basis. Another disclosure of unpredictability in the art of codon usage is that of Nagata et

al. (BBRC 261: 445-451 (1999)) wherein obstacles are summarized for the expression of genes in host mammalian cells on page 445, first paragraph after the abstract. Nagata et al. further describes an indication that codon study to clarify codon usage as related to polypeptide expression is known on page 445, second column lines 31-34. Nagata et al. was published years after issuance of the above cited Hatfield et al patent, and additionally documents the Hatfield disclosure as not being well known. Applicants cannot rely on a procedure in Hatfield et al as well known to assist in enabling the methods of claim 18 or 37.

Applicant may argue that inoperative subject matter is permitted in a claim and that generic polynucleotides what contain codons corresponding to encoding the polypeptides which are inoperative are thus permitted within the scope of the claim. Consideration, however, of the MPEP at section 2164.08(b) regarding inoperative embodiments reveals that the standard is whether a skilled person could determine which embodiments, that were conceived, but not yet made, would be inoperative or operative with no more effort than is usually required in the art. This argument, however, would not be persuasive as some type of operativeness test would reasonably be required in order to make this determination. As discussed above, the myriad of possible testing for active polypeptides reasonably would require undue experimentation itself. Normally in the art, a specific test would be required for polypeptide activity assessment even if cultured as described. Such a test is not apparent for assessment of operative vs inoperative polynucleotides and host cells for preparation of a useful polypeptide encoded by the sequences or sequences "that vary from SEQ ID NO: 302/303 due to differences in codon usage as a result of the degeneracy of the genetic code.".

This, in summary, the above described unpredictability for polynucleotide testing, or even what test to perform as well as host cell selection with corresponding codon, codon pair and/or codon context practice is supported by the number into enormous possibilities. No instant guidance to reasonable narrow the required experimentation leads to a determination of undue experimentation being required for both polynucleotide selection, and host cell selection that would result in an active and therefor useful polypeptide encoded by the elected sequences or variant thereof.

(2) – the amount or direction presented-

None other than the above described general knowledge in the art, which still leaves undue experimentation for enabling the instant invention. The specification provides the following definitions or explanations for "degenerate variants" or a sequence that varies from SEQ ID NO: 302/303 due to differences in codon usage as a result of the degeneracy of the genetic code of polynucleotides and polypeptides. At page 26 of the specification, "degenerate variants" are described as "encoding immunogenic polypeptides", taking into account "codon degeneracy, amino acid similarity, reading frame positioning and the like... variants will contain one or more substitutions, additions, deletions and/or insertions, preferable such that the immunogenicity of the polypeptide encoded is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein. The term "variants" should also be understood to encompass homologous genes of xenogenic origin." Further in the specification at page 30, "nonetheless polynucleotides that vary due to differences in codon usage are specifically contemplated... alleles of the genes comprising the sequences... that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function..."

(3)- the presence or absence of working examples-

No working examples have been presented to guide or enable the claimed polypeptides or methods of their use.

(4)- the nature of the invention-

The invention is complex as there is no guidance as to which activity, out of myriads possible to test for usefulness of 302 or 303 or degenerate variants thereof, once prepared. Even testing of polypeptide activity is generally a detailed process.

(5)- the state of the prior art-

Although many polypeptides have been cloned and expressed in culture, the Hatfield et al. summary indicates that the cultural expression of an active polypeptide is elusive and subject to many complex factors.

(6)- the relative skill of those in the art-

The cultural expression of polynucleotides in vectors in host cells to make a polypeptide is generally performed by graduate level or even more highly skilled individuals and is subject to

numerous complex considerations for successful results. Even with this skill level, an unsuccessful result is frequently obtained, as noted above by Hatfield et al.

(7)- the predictability or unpredictability of the art-

The factors for making a useful and thus enabled polypeptide with the claimed polynucleotides are elusive and unpredictable for a polypeptide wherein the polynucleotides which encode it for any host must be determined as described above.

(8)- the breadth of the claims-

The claims are directed to encompass polynucleotides of a particular sequence, or variants, substitutions, deletions or insertions therein. This is extremely broad regarding polynucleotides, vectors, and host cells that may be implemented in order to carry out the invention. As discussed above, the claim lacks any specificity as to what polynucleotides, vectors or host cells within this wide breadth of claim practice would be useable to result in the cultural making of an active polypeptide.

Thus, in conclusion, the above rejected claims lack enablement due to undue experimentation required to obtain the genus of claimed polynucleotides.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3, 4, 11, 15 and 18 are rejected under 35 USD 102(a) as being anticipated by FRUDAKIS WO 98/45328 (Previously made of record 11/14/2002. No copy supplied).

Claim 18 utilizes the terms a sequence that varies from SEQ ID NO: 302/303 due to differences in codon usage as a result of the degeneracy of the genetic code" which appears to include deletions, insertions, mutations, substitutions etc as outlined above. Claim 18 also recites "complements" of the sequences which are not necessarily full length. Claim 15 only

requires one "primers" of 10 nt or so from the polynucleotides described in claim 18. They do not need to amplify the full sequence.

Claims comprising the full length elected sequences were previously accorded the filing date of 4/9/1999. The following reference was published in October of 1998. This document also has a differing inventive entity. Therefore this rejection is proper under 102(a).

Frudakis (WO 98/45328) discloses the DNA molecule of SEQ ID NO: #188 which has significant identity to SEQ ID NO: 302 and 303. Frudakis specifically discloses polynucleotides, and primers from these sequences. This DNA molecules is deemed to meet the limitations of "degenerate variant", and/or complements of SEQ ID NO: 302 and/or 303. This Sequence also comprises at least 10 nt of SEQ ID NO: 302 and/or 303 and meets the limitation of the primer claim. It is noted that SEQ ID NO: 302 has a stretch of adenine molecules in a polyA tail.

***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (571) 272 0723

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, PhD can be reached on (571) 272 0718. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

MARY K. ZEMAN
PRIMARY EXAMINER
1631
12/21/05